☐ **1:** Anticancer Res 2001 Jan-Feb;21(1A):471-6 Related Articles, Books, LinkOut

Topoisomerase I-DNA covalent complexes in human colorectal cancer xenografts with different p53 and microsatellite instability status: relation with their sensitivity to CTP-11.

Lansiaux A, Bras-Goncalves RA, Rosty C, Laurent-Puig P, Poupon MF, Bailly C.

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The topoisomerase I poison CPT-11 has proved efficient for the treatment of untreated metastatic colorectal cancers (CRC) and those refractory to fluoropyrimidines. However, the interpatient variability is important. A previous in vitro study suggested that measurements of the level of topoisomerase I-DNA intermediates trapped by camptothecin may be useful to estimate the chemosensitivity of colon carcinoma cell lines. To verify this hypothesis, we developed an immuno-assay to detect covalent topoisomerase I-DNA complexes in a series of human colorectal cancers xenografted in nude mice. Six human CRCs were selected for their distinctive p53 and microsatellite instability (MSI) status. Tumour lysates, prepared from mice untreated or treated with CPT-11, were fractionated onto CsCl gradients to separate free and DNA-bound topoisomerase I by centrifugation. Interestingly, significant levels of DNA-topoisomerase I complexes were detected in the tumours most responsive to the treatment with CPT-11, irrespective of their MSI and p53 phenotypes. Our in vivo study fully agrees with the predictions from the in vitro data indicating that evaluation of topoisomerase I-DNA complexes would be useful to predict the response of CRC to a treatment with CPT-11.

PMID: 11299781 [PubMed - indexed for MEDLINE]

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☐ 1: Int J Oncol 2001 May;18(5):1061-9

Potentiation of antitumor activity of irinotecan by chemically modified oligonucleotides.

Agrawal S, Kandimalla ER, Yu D, Hollister BA, Chen SF, Dexter DL, Alford TL, Hill B, Bailey KS, Bono CP, Knoerzer DL, Morton PA.

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Co-administration of synthetic chemically modified oligonucleotides with irinotecan, a selective topoisomerase I inhibitor, provided a significant enhancement in the antitumor activity of irinotecan. The enhancement of antitumor activity of irinotecan with co-administration of chemically modified oligonucleotides was observed in several tumor models--pancreatic cancer (Panc-1), colon cancer (HCT-116) and melanoma (A375). Inhibition of tumor growth in all three models required the co-administration of irinotecan and chemically modified oligonucleotides, but was independent of the nucleotide sequence of the oligonucleotides. The potentiation of antitumor activity was dependent on the dose of irinotecan and chemically modified oligonucleotides administered. The enhancement of antitumor activity of irinotecan was also observed by co-administration of a phosphorothioate oligonucleotide, however, to a lesser extent than did chemically modified oligonucleotides, suggesting that metabolic stability of the oligonucleotide contributes to the enhancement of antitumor activity seen with irinotecan. The co-administration of dextran sulfate sodium with irinotecan showed insignificant potentiation of antitumor activity of irinotecan, suggesting that the enhancement of antitumor activity of irinotecan observed was not a result of polyanionic characteristic of oligonucleotides. Co-administration of irinotecan and chemically modified oligonucleotides did not result in increased toxicity in the tumor models studied. Potentiation of antitumor activity of irinotecan observed with co-administration of oligonucleotides suggests that the oligonucleotides affect the pharmacokinetics and/or metabolism of irinotecan. The use of chemically modified oligonucleotides together with irinotecan may increase the therapeutic index of irinotecan in cancer patients and continued development of such agents should be considered.

PMID: 11295057 [PubMed - indexed for MEDLINE]

Phase II study of irinotecan as first-line chemotherapy for patients with advanced colorectal carcinoma.

Firvida JL, Irigoyen A, Vazquez-Estevez S, Diz P, Constenla M, Casal-Rubio J, Valladares-Ayerbes M, Castellanos J, Rodriguez R, Balcells M.

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BACKGROUND: The objective of this multicenter, open-labeled, Phase II study performed in Spain was to assess the efficacy and safety of irinotecan (CPT-11) as first-line chemotherapy for patients suffering from advanced colorectal carcinoma (CRC). METHODS: Patients with histologically proven CRC and at least one bidimensionally measurable lesion, ages 18-70 years, with a performance status < or = 2, normal analytical values, and no prior chemotherapy or only adjuvant chemotherapy completed before study entry were selected. The treatment schedule was CPT-11 350 mg/m(2) intravenously administered once every 3 weeks. Both tumor response and toxicity were assessed using the World Health Organization and National Cancer Institute common toxicity criteria. Changes in performance status, weight, and symptoms also were measured. RESULTS: Sixty-five patients (44 chemotherapy-naive patients and 21 patients who completed prior adjuvant treatment) were enrolled. Of these, 24.7% of patients responded to the treatment, and 41.5% of patients had stable disease. Patients who had not received prior adjuvant chemotherapy had a lower rate of progression on therapy (27.3%) compared with those who had received prior adjuvant chemotherapy (42.9%). The median survival was 19.9 months (range, 0.3-29.3 months). No significant differences were found in the median survival between chemotherapy-naive patients and patients who had received previous chemotherapy. Grade 3-4 diarrhea and neutropenia were the most frequent severe toxic events, which were observed in 23.1% and 30.8% of patients and in 5.9% and 10.9% of the cycles, respectively. CONCLUSIONS: The current antitumor efficacy results show that 350 mg/m(2) of CPT-11 administered every 3 weeks is an active and feasible first-line chemotherapy regimen for patients with CRC. Finally, the overall safety data confirmed that CPT-11 is a well tolerated treatment. Copyright 2001 American Cancer Society.

☐ 1: Curr Oncol Rep 1999;1(2):155-60

Related Articles, Books, LinkOut

CURRENT reports

The role of irinotecan in colorectal cancer.

Saltz LB.

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Irinotecan, also known as CPT-11, is a topoisomerase I inhibitor currently approved for use as a second-line agent in the treatment of advanced colorectal cancer. Preliminary reports from randomized studies exploring combinations of CPT-11 plus 5-fluorouracil have shown improved antitumor activity versus 5-fluorouracil-based treatments alone, and suggest a first-line role for these combination regimens. The role of CPT-11/5-fluorouracil regimens in the adjuvant setting is now being actively explored. Studies of single-agent CPT-11 in the first-line treatment of metastatic colorectal cancer have shown activity; however response rates do not appear to be superior to those seen with standard first-line 5-fluorouracil-based regimens. The use of specific molecular markers as prognostic indicators of response or resistance to specific chemotherapies may, however, permit the identification of a selected population of patients with tumor characteristics that would specifically favor consideration of up-front use of single-agent CPT-11.

Publication Types:

- Review
- Review, Tutorial

PMID: 11122813 [PubMed - indexed for MEDLINE]

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1: Ann Oncol 2000 Oct;11(10):1323-33

Biweekly irinotecan or raltitrexed plus 6S-leucovorin and bolus 5-fluorouracil in advanced colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase II-III randomized trial.

Comella P, De Vita F, Mancarella S, De Lucia L, Biglietto M, Casaretti R, Farris A, Ianniello GP, Lorusso V, Avallone A, Carteni G, Leo SS, Catalano G, De Lena M, Comella G.

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PURPOSE: The aim of this randomised trial was to evaluate the activity and toxicity of a biweekly regimen including 6S-leucovorin-modulated 5-fluorouracil (LFA-5-FU), combined with either irinotecan (CPT-11 + LFA 5-FU) or raltitrexed (Tomudex) (TOM + LFA-5-FU), in advanced colorectal cancer patients, and to make a preliminary comparison of both these experimental regimens with a biweekly administration of LFA-5-FU modulated by methotrexate (MTX + LFA-5-FU). PATIENTS AND METHODS: One hundred fifty-nine patients with advanced colorectal carcinoma previously untreated for the metastatic disease (34 of them previously exposed to adjuvant 5-FU) were randomly allocated to receive: CPT-11, 200 mg/m2 i.v. on day 1, followed on day 2 by LFA, 250 mg/m2 i.v. infusion and 5-FU, 850 mg/m2 s i.v. bolus (arm A); TOM, 3 mg/m2 i.v. on day 1, followed on day 2 by LFA, 250 mg/m2 i.v. infusion and 5-FU, 1050 mg/m2 i.v. bolus (arm B); or MTX, 750 mg/m2 i.v. on day 1, followed on day 2 by LFA, 250 mg/m2 i.v. infusion and 5-FU, 800 mg/m2 i.v. bolus (arm C). Courses were repeated every two weeks in all arms of the trial. Response rate (RR) was evaluated after every four courses. The sample size was defined to have an 80% power to detect a 35% RR for each experimental treatment, and to show a difference of at least 4% in RR with the standard treatment if the true difference is 15% or more. RESULTS: The RRs were: 34% (95% confidence interval (95%, CI): 21%-48%) in arm A, including 3 complete responses (CRs) and 15 partial responses (PRs), 24% (95% CI: 14%-38%) in arm B, including 2 CRs and 11 PRs, and 24% (95% CI: 14%-38%), with 2 CRs and 11 PRs, in arm C. After a median follow-up time of 62 (range 18-108) weeks, the median time to progression was 38,

25, and 27 weeks for arm A, B, and C, respectively. With 94 patients still alive, the one-year probability of survival was 61%, 54%, and 59%, respectively. WHO grade 3 or 4 neutropenia and diarrhoea affected 46% and 16%, respectively, of patients treated with CPT-11 + LFA 5-FU. Median relative dose intensity over eight cycles (DI8) was 78% for CPT-11 and 82% for 5-FU. Severe toxicities of TOM + LFA-5-FU were neutropenia (16%) and diarrhoea (16%), but median relative DI8 was 93% for TOM, and 82% for 5-FU. CONCLUSIONS: CPT-11 + LFA-5-FU compares favorably in term of activity and toxicity with other combination regimens including CPT-11 and continuous infusional 5-FU. The hypothesis of a RR 15% higher than the MTX + LFA-5-FU treatment can not be ruled out after this interim analysis. The TOM + LFA 5-FU regimen showed a RR and a toxicity profile very close to the MTX + LFA 5-FU combination, and dose not deserve further evaluation in advanced colorectal cancer patients.

Publication Types:

- Clinical Trial
- Clinical Trial, Phase II
- Clinical Trial, Phase III
- Randomized Controlled Trial

PMID: 11106123 [PubMed - indexed for MEDLINE]

1: Anticancer Drugs 2000 Aug;11(7):573-8

In vitro sensitivity of human endometrial cancer cell lines to paclitaxel or irinotecan (CPT-11) in combination with other aniticancer drugs.

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We have evaluated the growth inhibitory effects of paclitaxel alone or irinotecan (CPT-11) alone and their combined effects with other drugs on human endometrial cancer cell lines. IC50 doses of paclitaxel (Tx), SN-38 (active metabolite of CPT-11; 7-ethyl-10-hydroxycamptothecin) and cisplatin, including other drugs which have been used for treatment of patients with endometrial cancer, were examined using five human endometrial cancer cell lines (Ishikawa, HEC-1A, HEC-50B, HEC-59 and HEC-108). When in vitro sensitivity was defined IC50 lower than 10% of the peak plasma concentration (PPC), all endometrial cancer cell lines were sensitive to paclitaxel and three of five endometrial cancer cell lines were sensitive to SN-38, whereas cisplatin was not active against any endometrial cancer cell lines used in this study. Regarding the other drugs, aclarubicin (ACR) and actinomycin D (ACD) were active against four of five endometrial cancer cell lines, etoposide (VP-16) and pirarubicin (THP) against two, and 5-fluorouracil (5-FU) against only one, while ifosfamide (4-OHIFO) was not active against any endometrial cancer cell lines. When combined effects of paclitaxel or SN-38 with other one drug were determined by the median-effect analysis, paclitaxel followed by cisplatin resulted in synergistic effects to all endometrial cancer cell lines. Paclitaxel followed by SN-38 also had synergistic effects to four cell lines. Sequential but not simultaneous administration of taxol and THP-adriamycin showed synergistic effects to three cell lines. In combinations of SN-38 with other drugs, simultaneous administration of SN-38 and cisplatin resulted in synergistic effects to all cell lines. It is noteworthy that ACD followed by SN-38 showed synergistic effects to all cell lines, and simultaneous treatment of ACD and SN-38 or SN-38 followed by ACD also resulted in synergistic effects to three cell lines. THP-adriamycin followed by SN-38 had synergistic effects to four cell lines. The present quantitative data analysis for synergism provides a basis for a rational design of clinical

protocols for combination chemotherapy in patients with endometrial cancer of the uterus.

PMID: 11036961 [PubMed - indexed for MEDLINE]

1: Cancer 2001 Feb 15;91(4):712-20

Irinotecan and chronomodulated infusion of 5-fluorouracil and folinic acid in the treatment of patients with advanced colorectal carcinoma: a phase I study.

Garufi C, Dogliotti L, D'Attino RM, Tampellini M, Aschelter AM, Pugliese P, Perrone M, Nistico C, Comis S, Terzoli E.

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BACKGROUND: Irinotecan (CPT-11) is an active drug in the treatment of patients with advanced colorectal carcinoma. The infusion of 5-fluorouracil (5-FU) according to circadian rhythms was used previously to decrease toxicity and to increase its therapeutic efficacy. The objective of this study was to establish the maximum tolerated dose (MTD) of CPT-11 together with a chronomodulated infusion of 5-FU and the l-form of folinic acid (FA). Secondary end points were the assessment of activity and quality of life (QoL). METHODS: Twenty-six patients with advanced colorectal carcinoma who had received previous treatment with 5-FU were entered on this Phase I study. At least three patients were recruited at each dose level. The CPT-11 starting dose was 175 mg/m(2) on Day 1 with an increase of 50 mg/m2 per dose level. A daily administration of chronomodulated 5-FU (900 mg/m2; peak delivery rate at 04:00) and FA (175 mg/m2; peak delivery rate at 04:00) for 5 days every 3 weeks was given with CPT-11. After the first three patients, the 5-FU dose was reduced to 700 mg/m2 per day due to toxicity. No intrapatient dose escalation was allowed. RESULTS: One hundred sixty-one courses were delivered. Dose-limiting toxicity was observed during the first course in seven patients (27%). Four patients developed neutropenia, with one patient reporting febrile neutropenia, two patients reporting severe stomatitis, and six patients reporting severe diarrhea. CPT-11 MTD was reached at 350 mg/m2 when a toxic death was observed with a recommended dose of 325 mg/m2. Six partial responses were observed (23%). The median duration of response and the progression free and overall survival rates were 199 days, 175 days, and 359 days, respectively. QoL was not affected by the treatment. CONCLUSIONS: The recommended dose for Phase II trials is 325 mg/m2 CPT-11 on Day 1, which is similar to the dose given as a single agent, together with a 5-day

chronomodulated infusion of 700 mg/m2 5-FU and 175 mg/m2 FA. Intensification of this schedule every 2 weeks should be achievable.

Publication Types:
- Clinical Trial
- Clinical Trial, Phase I

PMID: 11241238 [PubMed - indexed for MEDLINE]

☐ 1: Clin Cancer Res 1999 Jan;5(1):181-7

Antiangiogenic effects of camptothecin analogues 9-amino-20 (S)-camptothecin, topotecan, and CPT-11 studied in the mouse cornea model.

O'Leary JJ, Shapiro RL, Ren CJ, Chuang N, Cohen HW, Potmesil M.

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Angiogenesis has been correlated with increased invasion and metastases in a variety of human neoplasms. Inadequate inhibition of the growth of tumor microvessels by anticancer agents may result in treatment failure, rated clinically as progressive or stable disease. We have investigated the antiangiogenic properties of three camptothecin analogues, 9-amino-20(S)-camptothecin, topotecan, and camptosar (CPT-11), currently under investigation in clinical settings. Angiogenesis was induced by basic fibroblast growth factor in the cornea of inbred Swiss-Webster mice, with the aim of exploring the suppression of neovascularization by the analogues injected into the mice daily over a period of 6 days. The dose range chosen is known to inhibit, in the mouse model, the growth of various human tumor xenografts or murine tumors. The statistical analysis evaluated the association between the area of neoangiogenesis and the dose of the drugs tested and correlated the effects with observed drug toxicity. It was established that, as the drug doses increased, the area of neovascularization decreased, appearing to approximate a negative exponential curve. 9-Amino-20(S)-camptothecin at 6.89 and 8.26 micromol/kg (2.5 and 3.0 mg/kg) and topotecan at 8.31 micromol/kg (3.5 mg/kg), both drugs being delivered over a 6-day period, had statistically significant reduction (47.2-72.5%) of neoangiogenesis and acceptable toxicity. At higher doses of the two analogues, toxic body-weight losses and deaths were observed. CPT-11 showed statistically significant reduction of neoangiogenesis at a dose of 359 micromol/kg (210 mg/kg) delivered over a 6-day course. Unlike camptothecin analogues, the nontoxic dose of vincristine did not induce a statistically significant inhibition of angiogenesis, and there was no dose-dependent escalation of antiangiogenic effects. The results indicate that camptothecins are most likely cytotoxic against two tumor compartments: in

addition to tumor cells of epithelial origin, the drugs act against endothelial cells and prevent the growth of the tumor microvessels. We have hypothesized that treatment failure in some patients is due to incomplete or inadequate inhibition of the microvessel growth by camptothecins. Presumably, an intensive inhibition of the remaining tumor microvasculature in such patients could be achieved by combining a camptothecin with another antiangiogenic anticancer agent or with a highly selective angiogenic inhibitor exerting minimal dose-limiting toxicity. Such treatment by a camptothecin plus a less toxic inhibitor of angiogenesis can improve antitumor efficacy. To validate this concept, preclinical studies followed by clinical trials are planned.

PMID: 9918217 [PubMed - indexed for MEDLINE]
